

## *Review article: herbal treatment in gastrointestinal and liver disease—benefits and dangers*

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### SUMMARY

Herbal medicines are now used by up to 50% of the Western population, in a substantial minority of instances for the treatment or prevention of digestive disorders. Although most indications for the use of such remedies are anecdotally or traditionally derived, controlled trials suggest some benefits for ginger in nausea and vomiting, liquorice extracts in peptic ulceration, Chinese herbal medicine in irritable bowel

syndrome, opium derivatives in diarrhoea and senna, ispaghula and sterculia in constipation. Herbal preparations contain many bioactive compounds with potentially deleterious as well as beneficial effects.

There is clearly a need for greater education of patients and doctors about herbal therapy, for legislation to control the quality of herbal preparations, and in particular for further randomized controlled trials to establish the value and safety of such preparations in digestive and other disorders.

### INTRODUCTION

The terms alternative and complementary medicine denote theories and practices of medicine which deviate from the conventional, the former when they are used instead of, and the latter when they applied as an adjunct to standard management. The combined term, complementary and alternative medicine, encompasses a vast and heterogeneous range of diagnostic and therapeutic procedures as well as systematic and comprehensive concepts of health and disease.

The different types of non-conventional medicine may be divided into traditional and complementary groups (Table 1). The traditional group of complementary and alternative medicine contains the ancient practices of acupuncture, traditional Chinese medicine and Ayurvedic medicine, as well as manipulative osteopathy and chiropractice, and herbal and homeopathic medicine.

These are linked by long-standing traditions and are often used as the sole alternative treatment for all types of ailment or disease. The complementary group comprises more modern treatments that have been developed predominantly to act as complementary or additional to other forms of complementary and alternative medicine and scientific medicine.

The common denominator amongst all types of complementary and alternative medicine is their exclusion from the realms of conventional established scientific medicine, and consequently their sparse representation in research and teaching at universities. Alternative medicine practices are often based on ideas or beliefs which may ignore pathophysiological and pharmacological mechanisms identified by modern science, relying more on ancient practices and on 'natural' remedies, which are perceived as being less toxic than conventional drugs.

Most information relating to the possible effectiveness of alternative and complementary medicine is anecdotal or historical. Although there are very few controlled trials proving the beneficial effects of such practice in

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Table 1. Some different types of non-conventional medicine divided into traditional (often alternative) and complementary groups

Traditional	Complementary
Acupuncture	Aromatherapy
Traditional Chinese medicine	Biofeedback
Homeopathy	Detoxification
Herbal medicine	Reflexology
Ayurvedic medicine	Arts therapies
Osteopathy and chiropractice	Nutritional medicine
Hypnotherapy	
Faith healing	

any disease, over 30% of the Western population now use some form of complementary and alternative medicine. The single most commonly used modality in most Western surveys is herbal therapy.<sup>1–3</sup> Indeed, annual spending on herbal products by the general population is said to exceed £40 million per year in the UK and \$5 billion per year in the USA.<sup>1, 3</sup> These are extraordinary figures given the lack of scientific evidence about the efficacy or safety of herbal therapies in almost all the contexts in which they are used.

Doctors in general, and gastroenterologists in particular, can no longer ignore the potential benefits and dangers of herbal medicines. After an outline of the historical basis for the use of herbal remedies, the aims of this paper are to review data about their current usage by patients with digestive disorders, evidence for their efficacy in gastroenterological disease, the mechanisms by which they might act, and, lastly, their adverse effects on the gastrointestinal tract and liver. Attention will be focused on data obtained in human rather than animal studies.

## HISTORICAL BACKGROUND

Every culture has explored and used plants for medicinal purposes. The presence of several plants with medicinal properties in a Neanderthal tomb in Iraq suggests that herbs may have been used therapeutically for more than 60 000 years.<sup>4</sup> The first records come from China, where the Emperor Shen Nung compiled *Pen Tsao* (The Great Herbal, or Chinese *Materia Medica*) in about 3000 BC. This book had many subsequent editions, and many of the thousand or more drugs described are still used in China.<sup>5</sup>

The Ebers Papyrus, discovered in a tomb in Egypt in 1862, dates from 1550 BC and is the oldest medical text

to survive. It contains hundreds of herbal remedies, including castor seeds and senna for constipation, and a decoction of cumin, goose fat and milk for various stomach complaints.<sup>6</sup> Mesopotamian practice is recorded on a thousand clay tablets dating from the 7th Century BC: over 200 plant-derived medicines again included castor oil and senna as laxatives.<sup>6</sup>

More recently, Theophrastus (370–287 BC), a Greek botanist and pupil of Aristotle, and Dioscorides (40–90 AD), a Greek surgeon for Nero's army, each wrote text books describing the medicinal use of plants and their products.<sup>7, 8</sup> recommendations included cinnamon for internal inflammation and brambles for diarrhoea. Galen's (129–216 AD) enormous opus included a text on drugs, of which *hiera picra*, made from aloes, spices and herbs, achieved widespread use for constipation.<sup>6</sup>

The Hindu physician, Susruta, listed 760 medicinal plants in an Ayurvedic text in the 5th Century AD.<sup>5</sup> Towards the end of the first millennium, and influenced strongly by translations of Galen, Arabic medicine was intensely active, producing a number of plant-derived drugs, including laudanum and again senna.<sup>5</sup> At the same time, the first surviving Saxon medical manuscript, the *Leech Book of Bald*, described many herbal remedies and their indications:<sup>9</sup> it is a pity that the term 'Wortcunning' used to describe the contents of this book is neither genuinely archaic nor still in use as a synonym for herbalism.

The provenance of herbal medicine is thus extraordinarily diverse. Indeed, its trans-cultural origin and centuries of continuing use suggest that at least some of its constituents are likely to be of therapeutic value. This has become clear with the derivation from plants of a number of conventional drugs, including digoxin from foxgloves, aspirin from willow-bark, quinine from cinchona-bark and morphine from the opium poppy. Furthermore, pharmaceutical companies are now engaged in extensive screening programmes to identify and isolate therapeutically active agents from plants.

Despite these comments, the use of a herbal remedy for several thousand years does not of course guarantee either its efficacy or safety. The use of herbal preparations by the general population is still largely unsupported by either efficacy or safety data from clinical trials. In the context of gastroenterology, for example, usage for specific symptoms appears to be determined by unsubstantiated statements such as that appearing on

pots of slippery elm and in cookery books about fenugreek (methi seeds) that each 'soothes inflamed intestine'.<sup>10</sup> What proportion of the population, and in particular those with digestive problems, use herbal and other alternative or complementary therapies in the almost total absence of data to support their decision?

#### CURRENT USE OF HERBAL THERAPY BY PATIENTS WITH DIGESTIVE AND OTHER DISORDERS

Surveys of the general population of varying design and quality have shown that 8–50% of people in Western Europe and the USA have used some form of complementary therapy.<sup>11</sup> In developing countries, the usage is even more widespread.<sup>12</sup> Well-conducted random telephone surveys in the USA showed that the use of complementary and alternative medicine in the previous year rose from 34% in 1990 to 42% in 1997.<sup>1</sup> The single most widely used modality in 1997 was herbal medicine, which showed a 380% increase from 7 years earlier. The most common reason for the use of alternative or complementary therapies in general is relief from chronic musculo-skeletal disorders inadequately responding to conventional medicine, although for herbalists the case-mix tends more to eczema, headache and menstrual problems.<sup>11</sup> The typical user in the UK is female, aged 35–60 years and of a relatively high socio-economic group.<sup>11</sup> In the 1990 and 1997 US surveys, about 10% of complementary and alternative medicine use was for digestive complaints, with relaxation and herbal therapy most commonly employed for these indications.<sup>1</sup>

Several surveys have studied, specifically, the use of alternative and complementary therapies, including herbal remedies, by patients with gastrointestinal complaints (Table 2). For example in one survey, 9% of patients with digestive complaints consulted alternative practitioners for their symptoms, while in another, 51% of patients with gastrointestinal disorders had tried some form of complementary and alternative medicine.<sup>13, 14</sup> Complementary and alternative medicine for all digestive indications appears to be more popular in North America than Europe, although the growth of the industry in Europe is now probably faster. Herbal remedies are the single most used type of complementary and alternative medicine.<sup>15–17</sup> Usage is particularly common in patients with irritable bowel syndrome and inflammatory bowel disease;<sup>14–19</sup> this may be related to the chronic and refractory nature of these disorders as well as psychological factors.<sup>16, 17, 19</sup>

#### EFFICACY OF HERBAL MEDICINES IN GASTROINTESTINAL DISORDERS AND LIVER DISEASE

In this section, we shall discuss only controlled clinical trials (Tables 3 and 4) and omit such evidence where it relates to the conventional use of chemically extracted or newly synthesized plant constituents, for example morphine for abdominal pain.

##### Methods

A systematic literature search was undertaken using Medline database 1966–2001 records published either

Table 2. Prevalence of use of alternative and complementary therapies by patients with digestive disorders

Author	Year	Country	% use of CAM	Comments
Smart <sup>18</sup>	1986	UK	16%	Irritable bowel syndrome patients only
Sutherland <sup>13</sup>	1994	Canada	9%	Patients with gastrointestinal disorders treated by complementary and alternative medicine practitioner
Moser <sup>19</sup>	1996	Austria	33%	Increased use in patients with associated psychological factors
Moody <sup>15</sup>	1998	UK	20%	Comparison of use in European and Asian patients with inflammatory bowel disease
Hilsden <sup>16</sup>	1998	Canada	51%	Inflammatory bowel disease only
Rawsthorne <sup>14</sup>	1999	Canada, Ireland, USA	51%	Greater use in north American than Irish inflammatory bowel disease patients
Langmead <sup>17</sup>	2000	UK	26%	Increased use in patients with inflammatory bowel disease and poor quality of life

Table 3. Placebo-controlled trials of herbal therapies in patients with digestive disorders. For comparison the placebo response in trials using conventional therapy is also shown

Complaint	Herbal therapy trials				Conventional therapy trials	
	Herb	Treatment response rate	Placebo response rate	P-value	Placebo response rate	Reference
Constipation	Celandin, aloe vera, psyllium	**	**	$P < 0.02$	35%	Odes <sup>22</sup>
Post-operative	Cassia alata	83%	18%	$P < 0.001$	Incidence of nausea 40%	Thamlikitkul <sup>23</sup>
	Ginger	28%*	51%*	$P < 0.05$		Bone <sup>25</sup>
Nausea and vomiting	Ginger	21%*	41%*	$P < 0.006$	40–50%	Phillips <sup>26</sup>
	Ginger	36%*	22%*	N.S.		Arfeen <sup>27</sup>
	Ginger	53%*	33%*	N.S.		Visalyaputra <sup>28</sup>
Irritable bowel Syndrome	TCM	42%	22%	$P < 0.001$	40–50%	Bensoussan <sup>32</sup>
	Ayurvedic	65%	33%	$P < 0.001$		Yadav <sup>33</sup>
Peptic ulcer disease	Padma 179	77%	32%	$P < 0.001$	Up to 36%	Ligumsky <sup>34</sup>
	Curcuma	87%	53%	$P < 0.002$		Thamlikitkul <sup>40</sup>
Inflammatory bowel disease	Mastic gum	70%	22%	$P < 0.01$	Up to 40%	Al Habbal <sup>41</sup>
	Jian Pi Ling	53%	19%	$P < 0.01$		Chen <sup>47</sup>

\* Results expressed as incidence of nausea; \*\* Results expressed as change in symptoms from baseline rather than response rate.

Table 4. Placebo-controlled trials of herbal therapies for liver disease (N.S. denotes not significant)

Disorder	Herb	Outcome measures	P-value	Reference
Alcoholic liver disease	Silybum	Liver biochemistry	$P < 0.001$	Salmi <sup>52</sup>
		Liver histology	$P < 0.03$	
	Silybum	Progression over 3 months	N.S.	Trinchet <sup>53</sup>
	Silybum	Progression over 2 years	N.S.	
Cirrhosis (all causes)	Silybum	2 years survival	N.S.	Ferenc <sup>55</sup>
		4 years survival	$P < 0.04$	
		Incidence of HCC in 5 years	$P < 0.03$	
Acute viral hepatitis	Kamalahar	Liver biochemistry	$P < 0.001$	Oka <sup>59</sup>
Chronic hepatitis C	CH-100	Progression over 6 months	$P < 0.03$	Das <sup>56</sup>
		Viral clearance	N.S.	Batey <sup>57</sup>

in English or with English abstracts available. Search headings and key words used were combinations of: complementary medicine, gastroenterology, herbal therapy, constipation, peptic ulcer, irritable bowel syndrome, nausea, vomiting, inflammatory bowel disease, colitis, Crohn's disease, liver disease, hepatitis, cirrhosis, colorectal cancer and gastric cancer. Uncontrolled trials and animal studies are excluded from this report.

### Constipation

Plant extracts are commonly used in the conventional symptomatic approach to management of constipation. Anthraquinones are known to have stimulant laxative

properties and are present in senna and aloes (from the sap of aloe vera leaves). Dietary fibre produces a bulk-forming laxative effect, e.g. isphagula husk and plant polysaccharides can be used to increase stool water, e.g. psyllium.<sup>20, 21</sup> Many sufferers of constipation self-medicate and a number of other herbal remedies have been shown to be effective in controlled trials (Table 3).

A combination of celandin, aloe vera and psyllium was evaluated in 35 adults with chronic constipation in a double-blind placebo-controlled trial. After 2 weeks, a significant improvement in bowel frequency, stool consistency and laxative dependency was seen in the active treatment group compared with basal symptoms, with no such improvement seen in the placebo group.<sup>22</sup>

A Thai medical plant, *Cassia alata*, was tested against mist alba in a placebo-controlled, multicentre trial. Eighty patients were randomized into three groups and each received a blinded single dose of treatment. More patients in the cassia alata and mist alba groups had passed stools after 24 h than in the placebo group.<sup>23</sup>

Lastly, the Ayurvedic herbal remedy, Miskakasneham, was found to be as well-tolerated, effective and safe as a conventional senna-based laxative, Sofsena, in a controlled trial for the treatment of opiate-induced constipation in palliative care.<sup>24</sup>

Plants are very often used for relief and prevention of constipation both in dietary manipulation (e.g. extra rhubarb or spinach) and in specific remedies; clinical trial data would seem to support millennia of popular experience.

#### *Nausea and vomiting*

Ginger has been used as a remedy for nausea for centuries. It has been formally evaluated for the prevention and treatment of post-operative nausea and vomiting in four trials (Table 3). The first trial compared ginger with metoclopramide or placebo as an antiemetic after major gynaecological surgery. Ginger was superior to placebo in preventing nausea and vomiting and reducing the need for extra antiemetic.<sup>25</sup> In a similar design of trial, with the same three parallel groups, 120 patients were randomized to receive treatment before laparoscopic gynaecological surgery. The incidence of nausea and vomiting was higher in the placebo group than metoclopramide- or ginger-treated groups.<sup>26</sup> In contrast, in a study of 108 patients randomly allocated to receive ginger or placebo prior to laparoscopic surgery, there was no significant difference in symptoms of nausea or vomiting for 3 h post-operatively.<sup>27</sup> Most recently, a randomized controlled trial compared ginger alone, placebo, droperidol alone or droperidol plus ginger in 120 patients undergoing gynaecological laparoscopy. Again no significant difference in outcome was seen between any groups.<sup>28</sup>

There are two other controlled studies of ginger for nausea and vomiting. One is for the prevention of seasickness, in which 80 sea cadets received either ginger or placebo. The placebo group suffered significantly more symptoms of seasickness than the ginger-treated group.<sup>29</sup> In a crossover study of 27 women with hyperemesis gravidarum, there was a significant symptomatic benefit of ginger treatment over placebo.<sup>30</sup> A

systematic review of clinical trials of ginger for nausea and vomiting concluded that insufficient data exist as yet to establish whether ginger is efficacious.<sup>31</sup> Further formal studies of ginger for the relief of nausea in other settings, such as chemotherapy, are needed before conclusions can be drawn as to its universal effectiveness.

#### *Irritable bowel syndrome*

No conventional treatment is reliably effective in irritable bowel syndrome and it is unsurprising that up to 40% of patients with irritable bowel syndrome use alternative therapies.<sup>17, 18</sup> Herbal remedies are among the most common used by patients for this condition.

In one of the few double-blind, randomized controlled trials of traditional Chinese medicine to be published in the English literature, 106 patients with irritable bowel syndrome were randomized to one of the three treatments: individualized Chinese herbal preparations (prescribed specifically for individual patients according to diagnostic processes used in traditional Chinese medicine); a standardized Chinese herbal formulation (developed for general irritable bowel syndrome symptoms but not individual patients); and placebo, for 16 weeks (Table 3).<sup>32</sup> Bowel symptom scores were significantly improved in the active treatment groups compared with placebo. There was also a reduction in the degree of interference with life caused by irritable bowel syndrome symptoms. Individually tailored Chinese herbal remedies afforded no benefit over a standard herbal treatment at the end of the 16-week treatment period. However, at the end of a further 14 weeks of follow-up, the only group to show sustained improvement was that given individualized treatment.

In another double-blind randomized, placebo-controlled trial, a compound Ayurvedic preparation containing *Aegle marmelos correa* and *Bacopa monnieri* was compared with standard therapy (clonidine bromide, chlordiazepoxide and ispaghula) and placebo given for 6 weeks. Improvement occurred in 65% of the Ayurvedic treatment group, compared with 78% in the standard treatment group and 33% in the placebo group. Ayurvedic therapy was particularly effective for diarrhoea. At 6 months there was no difference in relapse rates in any group.<sup>33</sup>

Padma-179 is a Tibetan herbal medicine which was tested in a double-blind, placebo-controlled, randomized

trial of 72 patients for the treatment of constipation-predominant irritable bowel syndrome. There was significant benefit over placebo for abdominal pain, stool frequency, distension and flatulence as well as general well-being.<sup>34</sup>

In addition to these trials, which indicate a response of irritable bowel syndrome symptoms to several different herbal remedies, there are a number of trials of fibre preparations, such as isphagula husk and psyllium and also of peppermint oil.<sup>35, 36</sup> These will not be discussed here but do represent a crossing of the divide between alternative and conventional therapy in the management of irritable bowel syndrome.

#### *Peptic ulcer and chronic gastritis*

Liquorice has long been recognized as an ulcer-healing agent, and both carbenoxolone and deglycirrhizinated liquorice (Caved-S) were derived from this plant.<sup>37</sup> Other herbal treatments investigated for efficacy in peptic ulcer disease are capsaicin/chilli, mastic and curcumin.

The pungent ingredient of chilli, capsaicin is thought to have effects on substance P release and has been tested for its efficacy in peptic ulcer patients. The incidence of peptic ulcer varies between different ethnic groups in Singapore according to the amount of chilli used in the diet. In a case-control study of 103 patients with peptic ulceration, and 87 controls, median amounts of dietary chilli were significantly higher in controls than patients, indicating a possible protective effect of chilli ( $P < 0.001$ ).<sup>38</sup> Capsaicin itself has been shown to protect gastric mucosa against injury caused by 600 mg of oral aspirin in healthy volunteers in a blinded crossover study using 20 g of chilli vs. water ( $P < 0.05$ ), with gastroduodenal injury assessed by gastroscopy at 6 h.<sup>39</sup>

Another ingredient of curry, *Curcuma domestica* val, tested for its efficacy in dyspepsia in a placebo-controlled, double-blind, randomized trial of 116 patients, produced an 87% response after 3–6 months treatment, compared with 53% in the placebo group.<sup>40</sup>

Mastic, the resin from the trunk of the mastic or lentisc tree, was superior to placebo for ulcer healing in a randomized, double-blind, placebo-controlled trial of 38 patients with symptomatic duodenal ulcer.<sup>41</sup>

Wei yang an (WYA) is a Chinese herbal therapy used for peptic ulcer. Symptom scores, healing and relapse rates were examined in a controlled trial of WYA (135

patients) vs. cimetidine (104 patients) for peptic ulcer.<sup>42</sup> Symptomatic improvement (90% for WYA, 88% for cimetidine) and healing (60% and 67%, respectively) were similar in both groups, but the relapse rate at 1 year was significantly lower (59%) after WYA treatment than after cimetidine (84%;  $P < 0.05$ ).

Chinese journals also report many studies of herbal remedies for the treatment of chronic gastritis and intestinal metaplasia. Two controlled trials have demonstrated a significantly greater improvement in gastritis and intestinal metaplasia for MSJ-2D, a modified Sijunzi decoction (202 patients), and for piweiping capsule (143 patients), than occurred in placebo-treated subjects.<sup>43, 44</sup>

Given the morbidity caused by peptic ulcer disease and dyspepsia the world over, cheap and easily available treatments will always be in demand. The success of the spice ingredient, curcumin, has led to further investigation into its pharmacological effects (see later), but in developed countries herbal remedies are unlikely to compete effectively against H<sub>2</sub>-receptor blockers and, particularly, proton pump inhibitors.<sup>40</sup>

#### *Inflammatory bowel disease*

Much interest has been focused on the high prevalence of use of herbal medicines by patients with inflammatory bowel disease in published surveys, but very little controlled evidence exists for efficacy of any herbal remedy in inflammatory bowel disease.<sup>14–17, 19</sup>

Studies reported in Chinese literature refer to the treatment of ulcerative colitis with various herbal remedies, but often only abstracts are available in English. In a randomized controlled trial, 153 patients with ulcerative colitis received either Jian Pi Ling tablets and RSF-FS concoction enemas (group I), conventional treatment with oral 5-ASA and prednisolone enemas (group II), or oral placebo and RSF-FS enemas (group III).<sup>45</sup> Remission rates in group I were reported to be significantly higher (53%) than in groups II (28%) or III (19%), but the very low success rate of conventional therapy (group II) makes this study hard to interpret.

A trial of the traditional Chinese remedy, Kui jie qing (KJQ) studied 95 patients with ulcerative colitis given KJQ enemas four times daily for 20 days.<sup>46</sup> Eleven patients treated conventionally with sulfasalazine 1.5 g t.d.s., oral prednisolone 30 mg o.d., and prednisolone enemas 20 mg q.d.s. for 20 days were used as controls. Effective 'cure' was reported in 72% of KJQ-treated

patients compared with only 9% of controls ( $P < 0.001$ ). A further 23% of patients in the KJQ-treated group showed marked improvement compared with 53% in the controls, leading the authors to conclude a 95% effectiveness rate of KJQ, against 62% for conventional western treatment. In a similar trial, 118 patients with active ulcerative colitis were treated with Yukui tang ('decoction for ulcer healing') orally and herbal decoction enemas, plus oral prednisolone 15 mg o.d., mycifradin (an antibiotic) and vitamin B for 40 days.<sup>47</sup> Eighty-six control patients received prednisolone, mycifradin and vitamin B only. The overall effectiveness rate was 84% for the herbal therapy group (33% 'cured', 51% improved) and 60% for controls (17% 'cured', 43% improved;  $P < 0.01$ ). These last two studies suffer from a lack of randomization and blinding.

In India, the effect of the gum resin from *Boswellia serrata* in moderately active ulcerative colitis was compared to sulfasalazine: remission was achieved in 82% of the *Boswellia* group and 75% of those given conventional therapy ( $P = 0.2$ ).<sup>48</sup>

Although published data show limitations of trial design, some of these results, and the anti-inflammatory effects of a range of herbal therapies *in vitro* (see later), suggest a place for further formal studies of the efficacy of herbal therapy in both Crohn's disease and ulcerative colitis.

#### Liver disease

The most researched herbal treatment for liver diseases is *Silybum* or milk thistle. Its active constituents are collectively known as silymarin. *Silybum* has been reported in a number of uncontrolled studies and case reports as effective in the treatment of acute hepatic failure due to *Amanita phalloides* mushroom poisoning. In 18 patients, severity of liver damage was reduced according to the time to administration of *silybum*.<sup>49</sup> In a family of four with severe poisoning, the course of hepatic failure was improved by the addition of *silybum* to their therapy at day 3, when regular supportive treatment was failing.<sup>50</sup> In a retrospective study of 41 patients treated for *amanita* mushroom poisoning, the group that received intravenous silymarin treatment appeared to have a favourable outcome with no deaths.<sup>51</sup>

Other work has demonstrated possible hepatoprotective effects for silymarin in alcoholic liver disease. In 106 patients randomized to treatment with silymarin or

placebo, the treated group had a significant reduction in transaminases after 4 weeks, and improved liver histology (Table 4).<sup>52</sup> However, in a double-blind, placebo-controlled trial of 116 patients with moderately severe alcoholic liver disease, no benefit of silymarin treatment on progression of liver disease was seen over placebo after 3 months (Table 4).<sup>53</sup> This negative result is supported by a randomized, double-blind, placebo-controlled trial in 200 patients with alcoholic cirrhosis, in which silymarin had no effect on survival or course of liver disease (Table 4).<sup>54</sup> In contrast, in 170 patients with all causes of cirrhosis randomized to silymarin treatment or placebo, the 4-year survival rate in the treatment group was 58% compared with 39% in the placebo group (Table 4).<sup>55</sup> Although the results of these trials make it unlikely that silymarin will have a useful role in alcoholic liver disease, controlled trials of its efficacy may be worthwhile in other settings, including acute liver failure and chronic viral and auto-immune hepatitis.

A trial in acute viral hepatitis compared Kamalahar with placebo in 52 patients and again showed quicker and greater improvement in serum liver enzymes and bilirubin in the active treatment group.<sup>56</sup>

Trials of Chinese herbs in chronic liver disease include a placebo-controlled study of CH-100 in chronic hepatitis C, demonstrating a significant reduction in serum alanine transaminase over 6 months, but no clearance of the virus (Table 4).<sup>57</sup> Sho-saiko-to (SST) is a commonly used mixture of seven Chinese herbs. Its efficacy in 222 patients with chronic active hepatitis was studied in a placebo-controlled trial which showed that transaminases decreased significantly more in the SST group.<sup>58</sup> In another study in cirrhosis, a Sho-saiko-to remedy (TJ-9, a version of SST available commercially in Japan) was compared to conventional management for its effects on the incidence of hepatocellular carcinoma (HCC) in patients with cirrhosis of various causes. The two groups were matched for severity of liver disease, hepatitis B status, age and sex, and followed for 60 months. In a sub-group of patients who were negative for hepatitis B infection, there was a significantly lower incidence of hepatocellular carcinoma in the TJ-9 treated subjects (Table 4).<sup>59</sup>

Kuorinone is a matrine extracted from *Sophora Flavescens* ait. In a study of 94 patients with chronic hepatitis B, 45 patients received Kuorinone 400 mg intramuscularly daily for 3 months; 49 patients were given Interferon- $\alpha$ , 3 million units, subcutaneously

daily for 1 month followed by alternate days for 2 months. After 3 months, viral clearance was achieved in 60% of the kuorinone-treated group and 61% of the interferon-treated group.<sup>60</sup> This interesting result needs to be confirmed by larger, longer-term studies.

Stronger Neo-Minophagen C (SNMC) is a Japanese medicine containing glycyrrhizin, an aqueous extract of liquorice root. Its effects were reported in a retrospective study of 84 patients treated for chronic hepatitis C with SNMC for 2–16 years and 109 patients with similar disease treated with other herbal remedies for 1–16 years.<sup>61</sup> The two groups were compared with respect to incidence of hepatocellular carcinoma. The cumulative incidence of hepatocellular carcinoma over 15 years was significantly lower (12%) in the SNMC group than the controls (25%).

While these studies indicate promise for some herbal preparations for the treatment of liver disease, this organ, as indicated below, is particularly prone to serious and sometimes fatal adverse effects in patients taking herbal therapies.

#### POSSIBLE MECHANISMS OF ACTION OF HERBAL MEDICINES IN GASTROINTESTINAL DISEASE

##### *Placebo effect*

The placebo effect in clinical trials of conventional drugs in conditions such as irritable bowel syndrome and inflammatory bowel disease can be as high as 40% (Table 3).<sup>62</sup> It is conceivable that placebo responses to herbal medications will be at least as high in individuals strongly committed to the concept that such therapy will work.<sup>63</sup> On the other hand, patients with a strong preference for a particular treatment are less likely to enrol in placebo-controlled trials which may conversely effect the placebo response.<sup>64</sup> In a study aimed to address the issue of enhanced placebo response to herbal remedies, 21 healthy volunteers were given a physiologically neutral substance which they were led to believe would have arousal effects on temperature and pulse rate. In a crossover design, in one session the placebo resembled a traditional African herbal concoction, whereas in the other session it appeared to be a conventional Western style medication. No significant differences were seen in the strength of the placebo response.<sup>65</sup> In the only adequate placebo-controlled trial of Chinese herbal therapy in irritable bowel

syndrome, the placebo response was 22%.<sup>32</sup> Results from placebo-controlled herbal trials in inflammatory bowel disease and other gut disorders are awaited, but existing limited data do not support the hypothesis that the placebo response is enhanced in controlled trials of herbal medicine (Table 3).<sup>66</sup>

##### *Chemistry and bioavailability of herbal medicines*

Remedies derived from herbs contain a huge range of compounds, some common to many plants (for example pyrrolizidine alkaloids) and others specific to individual plants (see below). Aloe vera gel, the mucilage from the leaf pulp of aloe *Barbadensis* Miller, for example, contains at least 70 potentially biologically active compounds, including mono- and polysaccharides, amino acids, various enzymes including cyclo-oxygenase, antioxidant vitamins, minerals and salicylic acid.<sup>67</sup>

It is clearly difficult to extrapolate from a knowledge of the chemical composition of a given plant extract to its possible efficacy (or safety) *in vivo*. This will depend on a variety of factors including amounts of individual constituents in the extract (which may vary with the plant origin and method of preparation of the extract), interactions between individual constituents, and their pharmacokinetics, itself largely unstudied. In relation to the gastrointestinal tract, for example, some potentially active compounds such as polysaccharides may be active luminally, while others, such as antioxidant vitamins, may exert their effects systemically after absorption.

##### *Pharmacology of herbal medicines*

Extensive work of varying quality, clinical relevance and accessibility have suggested that, *in vitro* at least, individual chemicals derived from a variety of plants may have antibacterial, antioxidant, anticytokine, antispasmodic, cytotoxic and neuromodulatory actions.

For example, the anti-inflammatory actions of cat's claw, a Peruvian medicine used traditionally for digestive complaints and as an anti-inflammatory, have been studied *in vitro*. Cat's claw was found to inhibit oxidant-induced apoptosis in epithelial and macrophage cell lines, and lipopolysaccharide-induced iNOS expression and NFκB activation.<sup>68</sup> Curcumin has been shown to block cytokine-mediated NFκB activation and pro-inflammatory gene expression in stimulated Caco 2 cells.<sup>69</sup> Ginkgo biloba is a traditional Chinese herb now



commonly used for many indications including peripheral vascular disease and 'cerebral insufficiency'. Biological actions of ginkgo include inhibition of platelet activating factor,<sup>70</sup> and superoxide radical scavenging.<sup>71</sup> Lastly, slippery elm, fenugreek, devil's claw, Mexican yam, tormentil and Wei ting nong, a traditional Chinese herbal remedy, have all been found to have antioxidant effects *in vitro*.<sup>72</sup>

For reasons given above, however, extrapolation from such results to what may occur after ingestion of crude or purified plant extracts by patients with particular diseases cannot be undertaken reliably. There is a clear need for appropriately designed studies in man to assess the pharmacological actions, safety and ultimately clinical efficacy of the many herbal remedies of claimed but unproven benefit.

#### ADVERSE EFFECTS OF HERBAL MEDICINES ON THE GASTROINTESTINAL TRACT AND LIVER

Contrary to the widespread popular view that because it is natural it is safe, herbal therapy probably carries more risks and produces more serious side-effects than any other form of alternative therapy (Tables 5, 6 and 7).<sup>3, 73</sup> Unfortunately, there are no formal data on the incidence even of acute severe side-effects, such as liver failure after certain herbal medications, and knowledge of longer term sequelae such as mutagenicity and carcinogenicity is even more scanty. Table 5 shows a range of gastrointestinal side-effects which can be attributed to many different herbal therapies and Table 6 documents the wide range of herbs which have been reported to cause hepatotoxicity. A mandatory national systematic reporting scheme for the collection of adverse responses to herbs is highly desirable (see below).<sup>3, 74</sup>

##### *Direct side-effects and toxicity of herbal therapy*

The growing number of reports of serious adverse effects of herbal remedies on the liver include acute and chronic hepatitis, fulminant hepatic failure and possibly hepatic tumours.<sup>75</sup> While most of the adverse effects on the digestive tube are self-limiting and relatively trivial (Table 5), the same is not true of herb-induced hepatotoxicity, in which fatalities have been reported with alarming frequency.

Many different herbal medications have been implicated in hepatotoxicity (Table 6) and new culprits con-

tinue to be identified.<sup>76, 77</sup> Although in some cases specific herbal ingredients or chemicals, e.g. pyrrolizidine alkaloids, have been recognized as causative, usually the chemical compound responsible for the liver injury remains unknown.

Hepatic veno-occlusive disease was first described in 1951 in West Indians who drank herbal teas containing pyrrolizidine alkaloid. This compound is found in many herbs used in teas world-wide, especially those containing senecio, crotalaria and heliotropium.<sup>78</sup> Comfrey, which is very popular in teas, also contains pyrrolizidine alkaloids and has been associated with hepatotoxicity; it may additionally produce hepatomas and hepatosarcomas in animals.<sup>79</sup> Many other herbs have been implicated in cases of severe or fatal fulminant hepatitis and are listed in Table 6.

After reports of end-stage renal failure with aristolochic acid, an ingredient of some Chinese herbal medicines, the UK Committee for Safety of Medicines placed an emergency ban on import, sale and supply of aristolochic acid on 28 July 1999.<sup>91, 92</sup> Unfortunately, the same has not occurred with hepatic side-effects of herbal treatments and the public have to rely on herbal suppliers or practitioners to suspend voluntarily use of agents known to or thought to have toxic effects.

##### *Herb-drug interactions*

A further difficulty which formal evaluation and publicity might help avoid is the production of side-effects by the interaction of herbal medications with conventional drugs. Reports of herb-drug interactions are scarce and most lack adequate confirmation of herbal ingredients, or of blood concentrations of drugs or herbs or their metabolites to implicate a specific interaction. However, it is reasonable to assume that interactions between herbs and drugs may have toxic or important pharmacological effects (Table 7).<sup>93-100</sup> In relation to gastroenterology, it is likely that herbal treatments which affect gastrointestinal transit and absorption, for example psyllium or aloe sap, will have effects on the pharmacokinetics of oral drugs.

Some herbal treatments may interact with drugs used in the treatment of digestive disease, causing toxicity. For example, liquorice can enhance aldosterone-like effects of prednisolone leading to hypokalaemia and fluid retention. St John's wort enhances the activity of cytochrome P450 enzymes thereby increasing the

Table 5. Adverse effects of herbal remedies on gastrointestinal tract (data extracted from Chandler<sup>89</sup>)

Common name	Botanical name	Main use	Gastrointestinal side-effects	Suspected toxic ingredient
Feverfew	<i>Chrysanthemum parthenium</i>	migraine, menstrual problems, fever, worms	mouth ulcers	parthenolide
Anise	<i>Pimpinella anisum</i>	dyspepsia, carminative, cough	nausea, vomiting	anethole (oil)
Black cohosh	<i>Cimicifuga racemosa</i>	joint pains	nausea, vomiting	acetin, cimifugin
Fennel	<i>Foeniculum vulgare</i>	carminative, cough	nausea, vomiting	anethole (oil)
Gentian	<i>Gentiana lutea</i>	appetite stimulant, digestive aid	nausea, vomiting	gentiopicroin, amarogentin
Hydrangea	<i>H. arborescens</i> <i>H. paniculata</i>	diuretic, euphoric	nausea, vomiting	glycosides
Parsley	<i>Petroselinum crispum</i>	digestive aid, diuretic	nausea, vomiting	apiole and myristicin oils
Pau d'Arco	<i>Tabebuia</i> spp.	anticancer, antibacterial	nausea, vomiting	naphthaquinones
Pennyroyal	<i>Hedeoma pulegioides</i> , <i>Mentha pulegium</i>	carminative, abortifacient	nausea, vomiting, diarrhoea	pulegone oil
Poke root	<i>Phytolacca americana</i>	joint pains, constipation, cancer	vomiting, abdominal pain	phytolaccigenin
Senega	<i>Polygala senega</i>	cough	nausea, vomiting, diarrhoea	saponins
Tansy	<i>Tanacetum vulgare</i>	worms	nausea, vomiting	thujone oil
Aloes	<i>Aloe barbadensis</i>	constipation, irritable bowel syndrome	diarrhoea, abdominal cramps	anthraquinones
Senna	<i>Cassia acutifolia</i> <i>Cassia angustifolia</i>	constipation	diarrhoea, abdominal cramps	anthraquinones
Shavegrass	<i>Equisetum hyemale</i>	diuretic	diarrhoea	tannins, alkaloids
Yellow dock	<i>Rumex crispus</i>	constipation	diarrhoea, nausea	tannins, anthraquinones
Mistletoe	<i>Phoradendron tomentosum</i>	low blood pressure	abdominal pain	phoratoxins, tyramine
Mormon tea	<i>Ephedra nevadensis</i>	diarrhoea, tonic	constipation	tannin

degradation of drugs including ciclosporin.<sup>101–103</sup> Furthermore, herbal therapies can cause gastrointestinal side-effects as a result of drug interactions (Table 7). For instance, devil's claw and garlic increase prothrombin time in patients on warfarin, while, tamarind increases the bioavailability of aspirin; both effects may lead to gastrointestinal bleeding.

#### *The need for a licensing authority for herbal medicines*

The creation of a national body to license and control the use of herbs as medicines could allow the development of standards of preparation, content, safety testing, clinical trials and monitoring of treatment, as already occurs with conventional medicines. Such

Table 6. Adverse effects of herbal remedies on the liver

Common name	Botanical name	Main use	Liver injury	Reference
Herbal tea	<i>Senecio</i> and <i>Crotalaria</i>	tonic	veno-occlusive disease	McDermott <sup>78</sup>
Mistletoe	<i>Viscum album</i>	tension	hepatitis	Harvey <sup>80</sup>
Pennyroyal	<i>Hedeoma puleioides</i>	abortifacient	hepatitis	Sullivan <sup>81</sup>
Germander	<i>Teucrium chamaedrys</i>	obesity	fulminant hepatitis	Larrey <sup>82</sup>
Greater celandine	<i>Chelidonium majus</i>	diuretic	hepatitis	Benninger <sup>83</sup>
Chapparal	<i>Larrea tridentata</i>	anti-inflammatory	cholestatic hepatitis	Sheikh <sup>84</sup>
Kava	<i>Piper methysticum</i>	anxiety	fulminant hepatic failure	Escher <sup>85</sup>
Skullcap	<i>Scutellaria</i> spp.	stress	hepatitis	Macgregor <sup>86</sup>
Vallerian	<i>Valeriana officinalis</i>	stress	hepatitis	Macgregor <sup>86</sup>
Comfrey	<i>Symphytum</i> spp.	arthritis	veno-occlusive disease	Ridker <sup>87</sup>
Sassafras	<i>Sassafras albidum</i>	tonic	carcinoma	Segelman <sup>88</sup>
Chinese Herbal	<i>Paeonia</i> spp.	psoriasis	hepatitis	Kane, <sup>89</sup> Perharic-Walton <sup>90</sup>

Table 7. Interactions between herbal remedies and conventional drugs of relevance to gastroenterology<sup>79, 79, 88</sup>

Herb	Conventional drug	Consequence
<i>Interactions causing gastrointestinal side-effects</i>		
feverfew, garlic, ginseng,	warfarin	potentiation leading to GI bleeding
gingko, ginger, devils claw	iron	reduced absorption
St. John's wort	cyclosporin	reduced blood levels
echinacea	anabolic steroids, methotrexate,	hepatotoxicity
	amiodarone, ketoconazole	
tamarind	aspirin	potentiation leading to GI bleeding
inkcap	alcohol	disulfiram effect
<i>Interactions with herbs used in gastrointestinal disorders</i>		
chilli/capsaicin	ACE inhibitors	cough
psyllium	lithium	reduced blood levels
Shosaiko-to	prednisolone	reduced bioavailability and effectiveness
liquorice	spironolactone	antagonism of effect
	prednisolone	increased salt/water retention, hypokalaemia

standards could make a major contribution to maximizing the safety, as well as appropriate usage, of plants and their extracts in therapeutics. In the UK, the House of Lords ordered a Select Committee on Science and Technology to produce a report addressing these issues in complementary and alternative medicine. Published on 21 November 2000, the report recommends a change in practice of complementary and alternative medicine in the UK, particularly focusing on a regulatory system for complementary and alternative medicine professions, and on research and development plans to better establish safety and efficacy of complementary and alternative medicine practices (<http://www.publications.parliament.uk/pa/ld/ldsctech.htm>).

Side-effects of herbal medications which might be avoided if compulsory quality control was enforced, include those arising from use of the wrong (for example, misidentified) plant, and from adulteration of the preparation either by other toxic herbs or by non-organic contaminants, including heavy metals.<sup>2, 3, 100, 104</sup> These problems appear to be more common with herbs imported from outside Europe and North America.<sup>3</sup> More bizarrely, there have been several reports of the deliberate incorporation into plant extracts of conventional drugs such as indometacin, phenylbutazone and corticosteroids, each of which could have adverse effects on the gastrointestinal tract and elsewhere.<sup>100, 105</sup>

#### *Indirect adverse effects of herbal therapy*

Finally, the use of herbal therapy may be complicated by several indirect adverse effects.<sup>2</sup> People initially

consulting herbal practitioners may suffer from misdiagnosis and consequent delay in obtaining effective conventional treatment. Others may delay or forego appropriate conventional options in favour of ineffective unconventional ones. When expectations of alternative therapy are high, failure to obtain relief from symptoms, particularly if treatment has been expensive, could also be construed as an adverse effect.

#### CONCLUSIONS

There is an urgent need for further scientific assessment of the potential benefits and dangers of the huge range of herbal medications available. This fact was recognized by the creation by the National Institutes of Health in 1993 of the National Centre for Complementary and Alternative Medicine: its budget rose from \$2 million in 1993 to nearly \$70 million in 2000 (<http://nccam.nih.gov>). Herbal preparations used for medicinal purposes should require licensing by an independent national body in order to improve their quality and safety, and to ensure that claims of efficacy are validated by randomized controlled trials. The general public, as well as pharmacists, general practitioners and hospital doctors, should be aware, particularly, of the risks associated with the use of herbal remedies, whether on their own or in combination with other herbal or conventional medicines. The incorporation of a short course on alternative and complementary therapy in medical school curricula would help achieve this end.

Lastly, scepticism about herbal therapy should be laced with optimism. It is clear from the history of the

development of conventional drugs that the pharmaceutical industry is well-advised to continue in its extensive screening of plants from all over the world for new therapeutic agents with which to treat currently refractory disease.

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